

Clinical Pharmacology Review of Herceptin, 98-0369

Herceptin is a recombinant humanized MoAb that selectively targets HER2, the extracellular domain of the EGF receptor 2 protein. The MoAb is an IgG1 that contains human framework regions with the CDR of a murine antibody that binds to HER2. Herceptin binds with high affinity to the HER2 protein, inhibits proliferation of human tumor cells that over expresses HER2 in vitro and in vivo, and is a potent mediator of ADCC.

Clinical pharmacokinetics were studied in three Phase 1, three Phase 2, and one Phase 3 investigations in patients with metastatic breast cancer with tumors that over express the HER2 gene product. Both single dose and multiple dose kinetics were studied. Pharmacokinetic data were collected as part of clinical safety and efficacy trials and no clinical studies were conducted to specifically investigate special populations, pharmacokinetics profiles or formulation issues.

From data used to perform a pharmacokinetics stimulation analysis, a weekly dose of 100 mg was selected for study and found to provide trough levels within the serum levels thought efficacious (10 to 20 $\mu\text{g/ml}$ based on preclinical studies). A loading dose of 250 mg was added to the dosing regimen to attain the target levels more quickly. Experience in early clinical development suggested that rather than administer a fixed dose of 250 and 100 mg, a body weight adjusted dose of 4 mg/kg as a loading dose and 2 mg/kg as a maintenance dose would improve the consistency of response. Furthermore, a minimum target trough level of 20 $\mu\text{g/ml}$ was selected as the lower limit of serum levels to be maintained upon repeated dosing.

Although the mechanism of Herceptin clearance are not specifically established, the presence of shed antigen from the HER2 receptor is known to increase the clearance of Herceptin.

The following studies investigated the pharmacokinetics of Herceptin:

Phase 1 studies

1. H0407g: a single dose study of 10, 50, 100, 250, and 500 mg
2. H0452g: a multi-dose once weekly dosing regimen of 10, 50, 100, 250, or 500 mg
3. H0453g: a multi-dose once weekly dosing regimen of 10, 50, 100, 250 or 500 mg with cisplatin

Phase 2 studies

4. H0551g: multi-dose given once weekly dosing regimen of 250 mg loading dose and 100 mg maintenance dose

5. H0552g multi-dose given once weekly dosing regimen of 250 mg loading dose and 100 mg maintenance dose with cisplatin

Phase 3 studies

6. H0648g once weekly multi-dose study of 4 mg/kg loading dose and 2 mg/kg maintenance dose in patients given Herceptin and chemotherapy

7. H0649g once weekly multi-dose study of 4 mg/kg loading dose and 2 mg/kg maintenance dose in patients given Herceptin

Summary of Pharmacokinetics:

Single dose studies were conducted in Phase 1 and used to characterize the pharmacokinetic profile of the MoAb. In multi-dose studies conducted in Phase 2, only trough and peak samples were obtained. Peak samples were collected within 1-hour of the end of Herceptin infusion. In addition to quantifying levels of Herceptin, all serum samples were also analyzed for shed antigen and antibodies to Herceptin. In one Phase 2 study and one Phase 3 study, shed antigen was determined at various times which included pretreatment samples.

For serum levels of Herceptin, pharmacokinetic data were fit to either a 1 or 2 compartment model as determined by the best fit of the data to the regression line. AUC, Cl and C_{ss} (steady-state concentrations) were determined using noncompartmental methods. Trough and peak serum levels were observed samples without modification. Half-life was determined by a standard technique using the slope of the terminal elimination phase.

Various factors were found to modify the pharmacokinetics of Herceptin including dose and shed antigen. Early studies demonstrated that Herceptin clearance (Cl_t) decreased with increasing dose as shown in the tables below. Concomitantly, half-life (t_{1/2}) increased with decreases in Cl_t following increased dosage. Since the volume of distribution remained basically unchanged with increases in dose, it is likely that the changes in Cl_t and t_{1/2} reflect an alteration in the elimination pathways of the MoAb rather than the extent of distribution. However, steady state serum levels were found to rise upon repeated dosing without an observable change in clearance suggesting that later rises in serum levels which occurred with repeated dosing may be due to alterations in distribution rather than elimination.

Additionally, Phase 1 studies revealed that an increased clearance of Herceptin correlated with levels of shed antigen in patients. The association between shed antigen and Herceptin clearance was found to be continuous rather than a step function with a specific cutoff such as 500 ng/ml. Given the dose selected for Phase 3 and the rise in trough levels of Herceptin with repeated dosing, only about 9% of patients failed to

achieve a level of 20 µg/ml of Herceptin in a Phase 3 study. The percentage of patients with shed antigen levels > 500 ng/ml varied in the different studies between 0 and 24%. The highest percentage was observed in study H0452g and the lowest percentage in study H0453g. The Phase 2 study H0649g demonstrated an elevated level of shed antigen level of 6.3% of the patients.

Ninety-one per cent (177/195) of the patients given a maintenance dose of 2 mg/kg obtained a trough serum level of 20 µg/ml or higher at one or more sampling times as observed in H0649g over the first 8 weeks. Trough serum concentrations at week 8 in studies H0648 and H0649 were greater than predicted from simulations based on Phase 2 data which suggests that later changes occur in the pharmacokinetics of Herceptin upon repeated dosing. Serum concentrations achieved an observed steady-state level later (12 to 32 weeks) than would be predicted by their earlier pharmacokinetics (at approximately 4 weeks) due to unknown factors.

Serum levels were not found to be indicative of outcome in the clinical study, but any relationship of pharmacokinetics to patient outcome is likely confounded by several clinical factors such as disease burden and prior chemotherapy. No data are available regarding the possible relation between tumor burden, shed antigen and pharmacokinetics of Herceptin.

No pharmacokinetic interaction was observed clinically in Herceptin's pharmacokinetics when combined with cisplatin, doxorubicin or epirubicin plus cyclophosphamide, or paclitaxel. However, a nonclinical study in primates suggests that although the combination Herceptin with Adriamycin and Cytosan do not effect the pharmacokinetics of Herceptin or the chemotherapeutic agents, the pharmacokinetics of Herceptin are altered by Taxol. Studies conducted in monkeys suggests that Taxol decreases the Clt of Herceptin by almost 50% thereby increasing serum levels. The non-clinical study used a different dosing regimen than that used clinically as the non-clinical study used an iv bolus administration of Herceptin followed by a 60 minute iv infusion. No effect on Taxol pharmacokinetics were observed in combination with Herceptin in monkeys.

Based on clinical and non-clinical studies, changes in formulation did not influence the pharmacokinetics of Herceptin. Changing from a single-dose liquid to multiple-dose lyophilized formulation did not appear to change the pharmacokinetics of Herceptin as Cmax and AUC were found to be similar in patients given either formulation in a Phase 3 study (H0648g). Additional evidence for a lack of effect on the pharmacokinetics of Herceptin with changes in formulation or manufacturing was demonstrated in a series of non-clinical studies which were conducted using rhesus monkeys. These studies revealed no changes in pharmacokinetics incident to single dose vs multi-dose preparations, changes in the cell line used or scale-up for manufacturing purposes.

Tables which summarize the pharmacokinetics of Herceptin follow:

Dose, mg (mg/kg)	N	t1/2, hr (days)	Cl _t , ml/d/kg	V _d , ml/kg
10 (0.167)	9	36 (1.5)	26.5	53.6
50 (0.802)	9	103 (4.3)	10.3	51.5
100 (1.58)	9	155 (6.5)	7.5	55.3
250 (3.37)	10	242 (10.1)	5.72	48.5
500 (8.05)	11	373 (15.5)	5	65.6

Table of Summary of Pharmacokinetic Endpoints for Herceptin as a 90 Minute iv Infusion Across Studies H0452g, H0407g and H0453.

Dose, mg	N	t1/2, hr (days)	Cl _t , ml/d/kg	V _d , ml/kg	C _{trough} , ug/ml	C _{peak} , ug/ml
250/100	82	218 (9.1)	6.2	51	18.3	117

Table of Summary of Pharmacokinetic Endpoints for Herceptin given as 250 mg Loading Dose plus a 100 mg Maintenance Dose (once weekly) Given in Studies H0551g and H0552g. C_{trough}, C_{peak}, C_{ss} were averaged across all observations.

Dose, mg/kg	N	t1/2, hr (d)	Cl _t , ml/d/kg	V _d , ml/kg	C _{trough}	C _{peak}	C _{ss}
4/2	159	141 (5.9)	5.08	36.3	53.6	99.8	55.6

Summary of the Pharmacokinetics of Herceptin Averaged from Studies H0648g and H0649g. Study H0648 examined the effects of concomitant chemotherapy: doxorubicin or epirubicin plus cyclophosphamide or paclitaxel. No effect of chemotherapy on the pharmacokinetics of Herceptin was observed. C_{trough}, C_{peak}, C_{ss} were observed at week 8 of repeated dosing.

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